# Comprehensive Review of *BAP1* Tumor Predisposition Syndrome

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## Background

- *BRCA1-associated protein-1* (*BAP1*) tumor predisposition syndrome (*BAP1*-TPDS) is a rapidly developing area of medical research
- Germline mutations in this multifaceted autosomal dominant tumor suppressor gene predispose families to the development of uveal melanoma (UM), mesothelioma (MMe), cutaneous melanoma (CM), renal cell carcinoma (RCC), and possibly other cancers
- The molecular function of the gene as well as the clinical phenotype of the syndrome are still being clarified
- We sought to conduct a complete review of all published research into *BAP1*-TPDS to more thoroughly understand the clinical implications of *BAP1* mutations
- This information, in conjunction with phenotypic characteristics such as age of onset, disease aggressiveness and survival, can aid in the management, diagnoses, prognoses, and therapy of these patients and their families

## Methods

- A literature review was conducted on all peer-reviewed published articles on *BAP1* and its drosophila homolog, *Calypso*
- A search on PubMed was directed with the keywords “BRCA1 associated protein-1,” “BAP1,” and “Calypso”
- 77 articles pertaining to the human *BAP1* gene and its association with cancer were obtained. Of these, 24 articles described patients with germline *BAP1* mutations
- The articles were collated and data were extracted via an article-by-article systematic review
- Evidence was reviewed on:
  - Cancer types observed
  - Clinical features of cancers
  - Evidence supporting role of *BAP1* in tumor suppression

## Results

- A total of 167 individuals from 51 families carrying 48 *BAP1* mutations have been reported via blood and tumor DNA sequencing, and obligate carriers
- Researchers focusing only on particular cancers have pursued *BAP1* testing, creating an ascertainment bias
- UM, MMe, CM, and RCC are major phenotypes

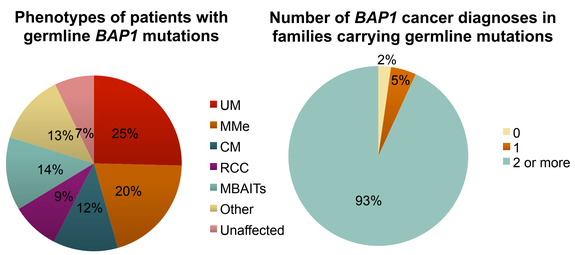
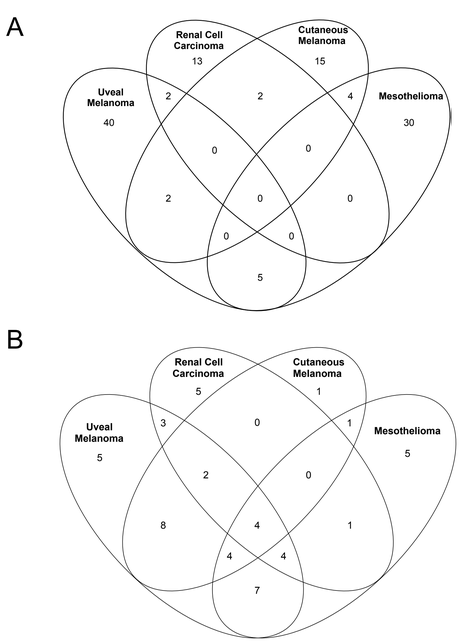



Figure 1: A. Germline *BAP1* mutation patients diagnosed with cancer B. Cancers reported in families with germline *BAP1* mutations




- Certain other cancers are also more commonly seen in patients with germline *BAP1* mutations (see figure 2)
- Cancers onset earlier in life
- Atypical Spitz tumors are also associated
- Tumors exhibit loss-of-heterozygosity
- Somatic mutations in sporadic tumors indicate *BAP1* involvement in tumor development

Figure 2: Germline and somatic data demonstrating *BAP1* involvement in cancer

| Tumor Type | Frequency in germline *BAP1* patients | Frequency in general population SEER | Median age of onset in germline BAP1 carriers (range) | Median age of onset in general population SEER | Biallelic inactivation shown in tumor, n | Report of somatic alteration in sporadic cancer | |
|---|---|---|---|---|---|---|---|
| | | | | | | Tumor DNA Sequencing | COSMIC Point Mutations |
| Uveal Melanoma | 49/167 (29%) | 0.001% | 51 (16-72) | 62 | Yes, 7 | 153/725 | 75/198 |
| Mesothelioma | 39/167 (23%) | 0.13% | 56 (34-85) | 74 | Yes, 7 | 162/406 | 81/260 |
| Cutaneous Melanoma | 23/167 (14%) | 3.25% | 46 (25-72) | 58 | Yes, 4 | 3/60 | 34/904 |
| Renal Cell Carcinoma | 17/167 (10%) | 1.60% | 47 (36-72) | 64 | Yes, 5 | 249/2483 | 117/1673 |
| Breast Cancer | 9/93 (10%) | 14.90% | 58 (37-85) | 61 | Yes, 2 | 0/45 | 11/1653 |
| Basal Cell Carcinoma | 11/167 (7%) | - | 50 (42-65) | - | Yes, 3 | | |
| Lung Cancer | 6/167 (4%) | 6.99% | 56 (46-59) | 70 | Yes, 1 | 2/77 | 13/1741 |
| Cholangiocarcinoma | 4/167 (2%) | 0.89% | 66 (47-71) | 50 | N/A | 44/502 | 12/1154 |
| Meningioma | 2/167 (1%) | - | 52 | 65 | Yes, 1 | | |

- Somatic *BAP1* mutations are characteristic of higher stage, more aggressive UM and RCC tumors
- Survival in RCC patients with somatic *BAP1* mutations is significantly decreased
- Somatic *BAP1* mutations characterize histologically distinct subset of UM, MMe, and RCC

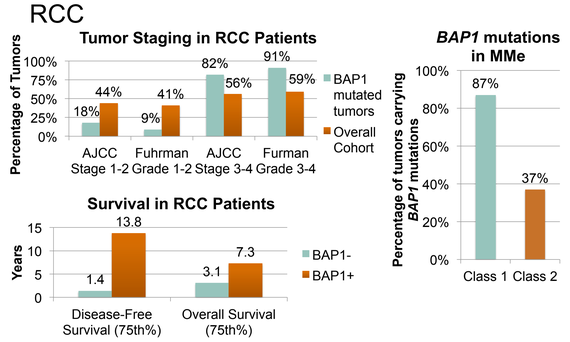
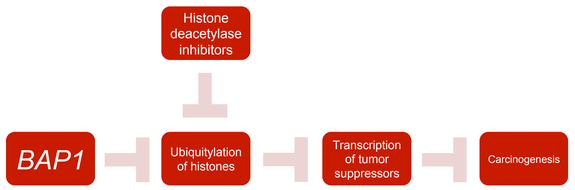



Figure 3: Proposed mechanism of action for histone deacetylase inhibitor therapies directed at *BAP1* tumors




## Summary

- *BAP1* testing is appropriate for patients with personal/family history of 2 or more UM, CM, MMe, or RCC (excluding family history of only multiple CM) in 1st or 2nd degree relatives
- Test 1st degree relatives for familial mutation

| Phenotypic Characteristics of *BAP1* mutation |
|---|
| Possible highly penetrant gene |
| Early age of onset |
| Tumors are more aggressive (except MMe) |
| Patients with MMe have lengthened survival |
| Histologically distinct tumors |
| Characteristic atypical Spitz tumors present |

| Risk | Management Recommendation |
|---|---|
| UM | Yearly ophthalmic screenings starting age 11. Nevi monitored biannually |
| CM | Yearly full body dermatological examinations starting age 20. Nevi monitored biannually |
| RCC | Yearly ultrasound scans and MRI every 2 years starting age 31. |

Potential histone deacetylase inhibitor therapies include valproic acid (VPA), trichostatin A (TSA), LBH-589 and Vorinostat (currently in Phase 2 trials for metastatic UM)

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References attached